Cystatin C predicts diabetic retinopathy in Chinese patients with type 2 diabetes

Sun, Shijie ; Li, Minglong ; Zhou, Jie ; Gai, Zhibo ; Shi, Haiyan ; Zhao, Qing ; Tian, Jun

Abstract: This study aims to identify the predictive value of cystatin C for diabetic retinopathy (DR) in Chinese patients with type 2 diabetes. Data from a cross-sectional hospital-based survey of 450 type 2 diabetes patients were analyzed in the study. DR was assessed by fundus fluorescein angiography. Duration of diabetes and other related information were obtained by questionnaire. Body mass index, blood pressure, HbA1c, cystatin C, glomerular filtration rate, urinary albumin excretion, blood lipids, and uric acid were measured. Binary logistic regression was performed to evaluate potential risk factors for DR. The predictive value of cystatin C for DR was evaluated using ROC curve. Cystatin C ($P = 0.039$) was a risk factor for DR after GFR, and other possibly related variables were adjusted. Cystatin C had a significant predictive value for any DR (AUC, 0.763, $P < 0.001$; optimal cutoff value, 1.11 mg/L; sensitivity, 56.00 %; specificity, 83.90 %) or severe DR (AUC, 0.821, $P < 0.001$; optimal cutoff value, 1.23 mg/L; sensitivity, 73.60 %; specificity, 88.70 %). Cystatin C is a novel risk factor for DR and should be used to screen and forecast the presence of DR (especially severe DR) in Chinese patients with type 2 diabetes. The association between cystiatin C and DR should not depend on the excellent ability of cystatin C for the estimation of GFR.

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Cystatin C Predicts Diabetic Retinopathy in Chinese Patients with Type 2 Diabetes

Shi-Jie Sun, MD[1,2], Ming-Long Li, MD[1], Jie Zhou, MD[1], Zhibo Gai, MD[3], Hai-Yan Shi, MD[4], Qing Zhao, MD[4], and Jun Tian, MD[5]

[1]Department of Endocrinology, Shandong Provincial Hospital affiliated to Shandong University, Shandong Clinical Medical Center of Endocrinology and Metabolism, Institute of Endocrinology and Metabolism, Shandong Academy of Clinical Medicine, Jinan, Shandong, China

[2]College of Medicine and Nursing, Dezhou University, Dezhou, Shandong, China.

[3]Department of Clinical Pharmacology and Toxicology, University Hospital，Zurich, Switzerland

[4]Diabetes Centre, Dezhou People's Hospital, Dezhou, Shandong, China

[5]Clinical Laboratory, Dezhou People's Hospital, Dezhou, Shandong, China

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Author information:

1. Shi-Jie Sun, MD

Department of Endocrinology, Shandong Provincial Hospital affiliated to Shandong University, Shandong Clinical Medical Center of Endocrinology and Metabolism,

Institute of Endocrinology and Metabolism, Shandong Academy of Clinical Medicine, Jinan, Shandong, China

College of Medicine and Nursing, Dezhou University, Dezhou, Shandong, China

Tel: +86-13053452675, Fax: 86-534 -898-5772, Email: dearsshjie@sina.com

2. Ming-Long Li, MD

Department of Endocrinology, Shandong Provincial Hospital affiliated to Shandong University, Shandong Clinical Medical Center of Endocrinology and Metabolism, Institute of Endocrinology and Metabolism, Shandong Academy of Clinical Medicine, Jinan, Shandong, China

Tel: +86-13793187151, Email: liminglong@medmail.com.cn

3. Jie Zhou, MD

Department of Endocrinology, Shandong Provincial Hospital affiliated to Shandong University, Shandong Clinical Medical Center of Endocrinology and Metabolism, Institute of Endocrinology and Metabolism, Shandong Academy of Clinical Medicine, Jinan, Shandong, China

Tel: +86-15168889772, Email: zhoujiepeking@163.com

4. Zhibo Gai, MD, PhD

Deartment of Clinical Pharmacology and Toxicology, University Hospital, Zurich Switzerland. Tel: +41-44-556-3000, Email: Zhibo.gai@usz.ch

5. Hai-Yan Shi, MD,

Diabetes Centre, Dezhou People's Hospital, Dezhou, Shandong, China

Tel: +86-13583496520, Email: shy7534@163.com

6. Qing zhao, MD

Diabetes Centre, Dezhou People's Hospital, Dezhou, Shandong, China

Tel: +86-13905343488, Email: qingzhao_sddz@163.com

7.Jun Tian, MD,

Clinical Laboratory, Dezhou People's Hospital, Dezhou, Shandong, China

Tel: +86-15605342002, Email: dztianjun@163.com

Address correspondence to:

Shi-Jie Sun, MD

Department of Endocrinology, Shandong Provincial Hospital affiliated to Shandong University, Shandong Clinical Medical Center of Endocrinology and Metabolism, Institute of Endocrinology and Metabolism, Shandong Academy of Clinical Medicine, Jinan, Shandong, 250021, China

Email: dearsshjie@sina.com

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Abstract

Background: Prediction of diabetic retinopathy (DR) is important in countries where systematic screening programs for diabetic eye disease have not been established. This study aimed to identify the predictive value of cystatin C for DR in Chinese patients with type 2 diabetes.

Subjects and Methods: Data from a cross-sectional hospital-based survey of 450 type 2 diabetes patients were analyzed in the study. DR was assessed by 7-field stereoscopic retinal photography. Duration of diabetes and other related information were obtained by questionnaire. Blood pressure, HbA_{1c}, cystatin C, glomerular filtration rate (GFR), urinary albumin excretion (UAE), and lipid were measured. Binary logistic regression was performed to evaluate potential risk factors for DR. The predictive value of related factors for DR was evaluated using ROC curve.

Results: Cystatin C (OR: 2.004, P=0.023) was a risk factor for DR after GFR and other possibly related factors were adjusted. Cystatin C had a significant predictive value for DR (AUC: 0.763, P<0.001; optimal cut-off value: 1.11 mg/L, sensitivity: 56.00%, specificity: 83.90%) or severe DR (AUC: 0.821, P<0.001; optimal cut-off value: 1.23 mg/L, sensitivity: 80.00%, specificity: 90.00%).

Conclusions: Cystatin C is a novel risk factor for DR, and should be used to screen and forecast the presence of DR (especially severe DR) in Chinese patients with type 2 diabetes. Moreover, the close association of cystatin C with DR does not depend on its superior ability in estimating GFR.

Introduction

Diabetic retinopathy (DR) is a severe complication of diabetes and the leading cause of visual loss and blindness in the working aged population [1-2]. Cystatin C is a small protein that belongs to the cysteine proteinase family, and is produced by all nucleated cells at a constant rate. Due to its small size, cystatin C can be filtered by the glomerulus freely, and it is not secreted but is fully reabsorbed and broken down by the renal tubules. This means that the level of blood cystatin C is primarily determined by the glomerular filtration rate (GFR). Studies have shown that cystatin C is a superior marker of GFR. A large number of studies have focused on the relationship between cystatin C and diabetic nephropathy (DN), but few studies have analyzed the relationship between cystatin C and DR. A recent study indicated that cystatin C is an independent risk factor for DR, and high cystatin C levels predict sight-threatening diabetic retinopathy (STDR) in type 2 diabetes patients [3]. STDR, including severe non-proliferative diabetic retinopathy (severe NPDR), proliferative diabetic retinopathy (PDR), and clinically significant macular edema (CSME) [4], greatly contributes to visual loss in patients with diabetes. Systematic screening programs for diabetic eye disease mainly aim to screen for STDR. By means of the screening programs, patients with STDR can be diagnosed early and receive appropriate treatment (for example, laser photocoagulation). This is helpful to protect patient's residual vision and to improve their quality of life. Unfortunately, in many developing countries, including China, the programs have not been developed. If cystatin C was capable of predicting STDR as reported, it could provide a promising

predictive parameter to doctors when they suggest that their diabetic patients should visit an ophthalmologist for further professional examination. However, existing epidemiological studies are insufficient for ascertaining the association between cystatin C and DR. DN and DR are microvascular complications of diabetes, and they have similar pathogenesis and risk factors. This indicates that the association between DN and DR should be close. Studies have found that cystatin C, as a superior marker of GFR, is a sensitive index to find the early phase of DN in patients with diabetes, especially in those diabetic patients with normoalbuminuria [5-6]. One study also found that lower estimated GFR was significantly associated with the severity of DR in Chinese patients with type 2 diabetes mellitus [7]. If there was a close association between cystatin C and DR, it is reasonable to speculate that the association is probably only because cystain C is a sensitive index to estimate GFR. Therefore, three problems are not clear and are worth exploring. First, it is not clear whether cystatin C is a real risk factor for DR. Second, it is not clear whether cystatin C has any value in predicting DR. Third, it is not clear whether or not the effect of cystatin C on DR is dependent on GFR. The aims of this study were to further evaluate the effect of cystatin C on DR, and to identify the predictive value of cystatin C for DR, as well as to evaluate whether the effect of cystatin C on DR is independent of GFR.

Subjects and Methods

Subject selection

Four hundred and fifty patients with type 2 diabetes were recruited from the Diabetes Centre of Dezhou People's Hospital from January 2012 to December 2013. Type 2 diabetes mellitus was diagnosed according to the 1999 World Health Organization criteria. The exclusion criteria of study subjects was as follows: (1) type 1 diabetes; (2) specific type diabetes or gestational diabetes mellitus; (3) with definite history of DR; (4) with acute complications of diabetes (such as infection or diabetic ketoacidosis); (5) with serious hepatic disease; (6) with acute or serious cardiovascular disease; (7) trauma or other definite causes and secondary nephropathy (such as glomerular nephritis, pyelonephritis, nephrolithiasis, or lupus nephritis); (8) retinopathy caused by hypertension; (9) with contraindications to perform ^{99m}Tc-DTPA dynamic renal imaging. The study was approved by the Human Research and Ethics Committee of Dezhou People's Hospital, and all participants signed informed consents that adhered to the tenets of the declaration of Helsinki.

Data collection and Measurements

Information on gender, age, duration of diabetes, family history of diabetes, history of smoking, history of hypertension, and history of DR were obtained using a questionnaire. According to 7-field stereoscopic retinal photography, patients were classified as: no diabetic retinopathy (NDR); mild non-proliferative diabetic retinopathy (mild NPDR); moderate non-proliferative diabetic retinopathy (moderate NPDR); severe DR, including severe NPDR or PDR [8]. Blood pressure was measured. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg,

diastolic blood pressure (DBP) ≥90mmHg, or with definite history of hypertension. Venous blood samples were drawn from all patients after an overnight fast. The concentration of serum cystatin C was measured by a highly sensitive latex-enhanced immunoturbidimetric method. GFR was assessed using ^{99m}Tc-diethylene triamine pentaacetic acid (DTPA) dynamic renal imaging (Gates method). Low-pressure liquid ion exchange and a flowing colorimetric method were performed to measure glycosylated hemoglobin (HbA_{1c}). Total cholesterol (TC) and triglyceride (TG) were measured by an enzyme-coupling colorimetric method. High-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were measured by a direct method. An immunoturbidimetric method was used to measure apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), and UAE. The ratio of AopA1/ApoB was calculated.

The continuous variables were categorized in the following way: Age（years）: <40, ~40, ~50, ~60; Duration of diabetes (years): <5, ~5, ~10, ~15; HbA1c (%) : <7.5, ~7.5, ~9.0, ~10.5, ~12.0; GFR (ml/min/1.73m^2): ≥90 (normal), 60－89 (slight decrease), 30－59 (moderate decrease), ≤29 (severe decrease or end-stage chronic kidney disease) [9]; cystatin C (mg/L): <0.80, ~0.80, ~1.00, ~1.20 (categories were based on quartiles); UAE: (mg/24 h): <30 (normoalbuminuria), 30－300 (microalbuminuria), ≥300 (macroalbuminuria) [10]. Lipids were categorized according to the National Cholesterol Education Program, Adult Treatment Panel (NCEP APT) [11]: TC (mmol/L): <5.2, ≥5.2; TG (mmol/L): <1.7, ≥1.7; HDL-C (mmol/L): >1.0, ≤1.0；

LDL-C (mmol/L): <2.6, ≥2.6. ApoA1/ApoB: ≥1.4, 1.2-<1.4, 1.0-<1.2, 0.8-<1.0, <0.8；

Statistical Analysis

Continuous variables were tested for normal distribution by the Kolmogorov–Smirnov test. The normal distributed continuous variables are described as the mean ± SD, and those non-parametrically distributed are shown as the median (inter-quartile range). Discrete variables are presented as frequencies (percentages). Comparisons of the groups for normally distributed continuous variables were performed by one-way ANOVA. The comparison of discrete variables was performed by the Chi-square test (R×C tables). Binary logistic regression was performed to evaluate the risk factors of DR. The variables that were proven to be significant in the univariate analysis were entered (method: Forward: LR) as independent variables in the regression model. Bivariate correlation analysis of Spearman was performed to evaluate the correlation between cystatin C and the severity level of DR. The ability of related factors in predicting DR was evaluated using a ROC curve. All statistical analyses above used SPSS 16.0. Statistical Software ROCKIT0.9β was performed to assess the difference of area under the ROC curve (AUC). All *P*-values were two-sided, and a *P*-value of <0.05 was considered statistically significant.

Results

Four hundred and fifty patients including 267 males (59.33%) and 183 females (40.67%) were involved in this study. The mean age was 55.17±10.32 years old, and the median (inter-quartile) duration of diabetes was 6.00 (2–11) years. Of the 450 patients, 60 (13.33%) had mild NPDR, 51 (11.33%) had moderate NPDR, 39 (8.67%) had severe NPDR, and 21(4.67%) had PDR. The prevalence of DR was 38.00%.

Between patients with and without DR, there were significant differences in age, duration of diabetes, hypertension, $HbA_{1c,}$ cystatin C, GFR, UAE, TC, TG, LDL-C, and ApoA1/ApoB (all $P<0.01$; Table 1). Of these variables, duration of diabetes, HbA_{1c}, cystatin C, hypertension, GFR, and ApoA1/ApoB retained their significant associations with the presence of DR in the binary logistic regression model (all $P<0.05$; Table 2).

The serum concentration of cystatin C was significantly different among patients with different severity levels of DR ($F=12.667$, $P<0.001$), and an increasing tendency of the concentration of cystatin C was shown with the increase in the severity level of DR (Fig. 1). There was a positive correlation between cystatin C and the severity level of DR ($r=0.534$, $P<0.001$; Table 3).

Cystatin C (AUC: 0.763, $P<0.001$, 95%CI: 0.681–0.846), duration of diabetes (AUC: 0.787, $P<0.001$, 95%CI: 0.708–0.865), and HbA_{1C} (AUC: 0.714, $P<0.001$, 95%CI: 0.629–0.800) had significant value in predicting DR (Fig. 2). The optimal cut-off value of cystatin C in predicting DR was 1.11 mg/L (sensitivity: 56.00%, specificity: 83.90%, Yoden index: 0.40). There were no significant differences for the AUC between cystatin C, HbA1c, and duration of diabetes ($P>0.05$; Table 4).

Cystatin C was significant (AUC: 0.821, P<0.001, 95%CI: 0.692–0.950) for predicting the presence of severe DR (severe NPDR or PDR), and the optimal cut-off value was 1.23 mg/L (sensitivity: 80.00%; specificity: 90.00%, Yoden index: 0.70) (Fig. 3).

Discussion

This study found that cystatin C was a risk factor for DR after GFR and other potentially related variables were adjusted. The morbidity of DR increased by 2.004 times with every 0.2 mg/L increase in cystatin C. This suggests that cystatin C is a stronger risk factor of DR, and the close association of cystatin C with DR does not depend on its superior ability in estimating GFR. However, why there is a close association between cystatin C and DR is not clear. The pathophysiologic changes of DR include edema of the macula, retinal inflammation, neovascularization, and optic neuropathy [12-15], and cystatin C likely plays an important role in these pathophysiologic changes. Retinal pigment epithelium (RPE) was identified as a major site for secretion of cystatin C, which is involved in the mechanisms of macular degeneration [16]. The neuroretina was found to be a high-affinity system, and human cystatin C injected intravitreally into normal rat eyes can be taken up into cells of the neuroretina and into the retinal pigment [17]. We speculate that there is perhaps a similar system in humans through which higher serum cystatin C could be taken up into the retinal pigment. Cystatin C plays an important role in inflammation and increases the levels of C-reactive protein (CPR) [18] and homocysteine (Hcy) [19],

which is involved in the impairment of the microvasculature. Cystatin C is also speculated to be involved in arterial wall remodeling, blood vessel integrity, neovascularization, and neuronal degenerative pathology [20]. These mechanisms mentioned above, involving cystatin C and DR, might partly explain the close association between them. Increasing evidence shows that traditional risk factors (such as diabetes duration and HbA_{1c}) do not fully explain a patient's risk of having DR [21]. Our findings indicate that cystatin C is a novel risk factor for DR, which probably partly solves this question.

It has been well established that duration of diabetes and the control of glucose are the strongest risk factors for DR, but there were no significant differences when the AUCs were compared between cystatin C, duration of diabetes, and HbA_{1c} in our study. This indicates that the ability of cystatin C in predicting DR should be superior. However, the optimal cut-off value (1.11 mg/L) is not ideal. Despite the higher specificity (83.90%), the sensitivity (56.00%) is lower. In our study, cystatin C had a more ideal cut-off point in predicting severe DR. Sensitivity and specificity were 80.00% and 90.00%, respectively, when the optimal cut-off point was 1.23 mg/L. This indicates that cystatin C seems to be a better predictive marker for severe DR and higher cystatin C levels are more capable of discriminating severe DR in patients with type 2 diabetes mellitus. This study found that cystatin C significantly correlated with the severity level of DR, and this probably explains why cystatin C was superior in predicting severe DR. DR, especially severe DR, can result in severe and irreversible visual loss. Except for common treatments (such as strict control of blood

glucose, and blood pressure and lipids), laser photocoagulation is the first and most effective option for treatment for DR. The Early Treatment Diabetic Retinopathy Study (ETDRS) showed that laser photocoagulation can reduce the progression of DR [22] and the risk of vision loss from PDR [23]. ETDRS also examined the effect of treating eyes with mild NPDR to early PDR, and suggested that scattered photocoagulation could be deferred at the stage of mild-to-moderate NPDR because the rate of visual loss was low with either treatment of photocoagulation applied early or delayed. When DR is more severe, photocoagulation should not be delayed. Therefore, early diagnosis of severe DR is very important for initiating effective laser photocoagulation. However, systematic screening programs for diabetic retinopathy have not been developed in many developing and poor countries (including China). Many diabetic patients with severe DR cannot be diagnosed in time, and so they do not undergo timely and effective treatment (especially laser photocoagulation). This results in the progression of visual loss, and even blindness. In fact, most of the patients with diabetes always visit an endocrinologist, but not an ophthalmologist unless their eyes have significant visual abnormality. Therefore, it is critical that endocrinologists suggest their patients visit an ophthalmologist to find existing DR, especially severe DR. It is helpful for those patients with severe DR to avoid further visual loss by means of the early diagnosis and appropriate initiation of photocoagulation. According to the optimal cut-off point of cystatin C in predicting severe DR, a concrete predictive index should be provided to endocrinologists when they suggest their patients with type 2 diabetes visit an ophthalmologist for further

professional examination. Moreover, the measurement of cystatin C is more convenient and economical than retinal photographs. Considering the growing financial burden of diabetes, cystatin C may be a promising biomarker in screening and forecasting the presence of severe DR.

In our study, the morbidity of DR increased by 3.823-fold with every 30 ml/min/1.73m^2 decrease of GFR. This indicates that GFR is an important protective factor for DR. The decrease of GFR is characteristic of diabetic nephropathy, and loss of GFR often occurs before the onset of microalbuminuria in type 2 diabetes mellitus [24]. Most previous studies only used albuminuria as a criterion to evaluate the existence of DN, which probably underestimated the association between DN with DR. Our study also found that the ratio of ApoA1/ApoB was significantly associated with DR. The morbidity of DR increased by 2.552-fold with every 0.2 decrease in the ratio of ApoA1/ApoB in our study. This suggests that serum ApoA1/ApoB measurement could be a new index of DR progression. Recently, several studies revealed that ApoA1, ApoB, ApoA1/ApoB, or ApoB/ApoA1 were significantly associated with DR [25-27]. TG, TC, or LDL-C did not show any significant associations with DR in a logistic regression model, which indicates that ApoA1/ApoB is probably more important than these lipid constituents in the progression of DR.

It is well known that duration of diabetes, the control of glucose and blood pressure are the traditional risk factors for DR [28]. Our study also found that duration of diabetes, HbA_{1c}, and hypertension were significantly associated with DR. The

morbidity of DR increased by 2.030-fold with every increase of 5 years' disease duration, and by 2.169-fold with every 1.5% increase in HbA_{1c}. Compared with diabetic patients without hypertension, 3.588 folds increase in patients accompany with hypertension. This further indicates that they play very important roles in the occurrence and progression of DR.

One advantage of this study was the rigorous inclusion criteria of subjects, which decreased the disturbance of some related confounding factors. However, the cross-sectional nature of the study limits the sequential of our finding. Moreover, the single source of study subjects is also a limitation. Subjects of this study only came from one diabetes center, which perhaps resulted in the number of severe DR (especially severe PDR) being less because many patients with severe DR visited the department of ophthalmology. This probably underestimated the association between cystatin C and DR. More epidemiologic (especially multicenter studies and prospective studies) and pathophysiological studies should be designed so that the association of cystatin C with DR can be confirmed.

In conclusion，cystatin C is a novel risk factor for DR, and should be used to screen and forecast the presence of DR (especially severe DR) in Chinese patients with type 2 diabetes. Moreover, the close association of cystatin C with DR does not depend on its superior ability in estimating GFR.

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Table 1. Characteristics of NDR and DR subjects.

Variables	*NDR (n=279)*	*DR (n=171)*	χ^2	*P value*
Gender (male/female)	168/111	99/72	0.237	0.627
Age (group 1/2/3/4)	33/60/90/78	6/24/72/87	25.75	0.000
Duration of diabetes (group 1/2/3/4)	168/84/18/12	33/45/42/48	112.00	0.000
Family history of diabetes (no/yes)	174/105	99/72	0.888	0.346
Hypertension (no/yes)	144/135	54/117	17.27	0.000
History of smoking (no/yes)	201/78	117/54	0.671	0.413
HbA_{1c} (group 1/2/3/4/5)	57/87/72/51/12	9/39/33/48/42	62.10	0.000
Cystatin C (group 1/2/3/4)	84/108/75/12	12/36/39/84	137.40	0.000
GFR (group 1/2/3/4)	225/72/8/2	64/42/27/10	61.65	0.000
UAE (group 1/2/3)	114/128/27	21/75/75	84.22	0.000
TC (group 1/2)	189/90	93/78	8.084	0.004
TG (group 1/2)	174/105	90/81	4.143	0.042
LDL-C (group 1/2)	219/60	114/57	7.709	0.005
HDL-C (group 1/2)	171/108	105/66	0.001	0.981
ApoA1/ApoB (group 1/2/3/4/5)	21/104/100/41/13	3/25/80/46/17	41.387	0.000

Age (years): group 1: <40, group 2: ~40, group 3: ~50, group 4: ~60; Duration of diabetes (years): group 1: <5, group 2: ~5, group 3: ~10, group 4: ~15; HbA1c (%): group 1: <7.5, group 2: ~7.5, group 3: ~9.0, group 4: ~12.0; GFR (ml/min/1.73m^2): group 1: ≥90, group 2: 60–89, group 3: 30–59, group 4: ≤29; Cystatin C (mg/L): group 1: <0.80，group 2: ~0.80，group 3: ~1.00, group 4: ~1.20; UAE: (mg/24 h):

group 1: <30, group 2: 30–300, group 3: ≥300; TC (mmol/L): group 1: <5.2, group2: ≥5.2; TG (mmol/L): group 1: <1.7, group 2: ≥1.7; HDL-C (mmol/L): group1: >1.0, group 2 ≤1.0; LDL-C(mmol/L): group 1: <2.6, group 2: ≥2.6. ApoA1/ApoB: group 1: ≥1.4 , group 2: 1.2-<1.4, group 3: 1.0-<1.2, group 4: 0.8-<1.0, group 5:<0.8. NDR, no diabetic retinopathy; DR, diabetic retinopathy; $HbA_{1c,}$ glycosylated hemoglobin; GFR, glomerular filtration rate; UAE: urinary albumin excretion; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B.

Table 2. Associations of risk markers with DR (binary logistic regression model).

Variables	*Measurement*	*OR (95.0% CI)*	*P value*
Duration of diabetes	Per SD (5 years) increase	2.030（1.203, 3.425）	0.008
HbA_{1C}	Per SD (1.5%) increase	2.169（1.370, 3.433）	0.001
Cystatin C	Per SD (0.2mg/L) increase	2.004（1.103, 3.643）	0.023
ApoA1/ApoB	Per SD (0.2) decrease	2.552（1.378, 4.727）	0.003
GFR	Per SD (30 ml/min/1.73m^2) decrease	3.823（1.541, 9.487）	0.004
Hypertension	No or Yes	3.588（1.162, 11.077）	0.026

Model simultaneously contained age, duration of diabetes, hypertension, $HbA_{1C,}$ cystatin C, GFR, UAE, TG, TC, LDL-C, and ApoA1/ApoB. age, UAE, TG, TC, and LDL-C were not in the equation of the binary logistic regression model at the last step (all P>0.05). HbA_{1c}, glycosylated hemoglobin; GFR, glomerular filtration rate; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B.

Table 3. Frequency distribution of DR with different severity levels among groups of cystatin C.

Cystatin C (mg/L)[a]	*NDR*	*Mild NPDR*	*Moderate NPDR*	*Severe DR* [b]
<0.80	84 (87.50%)	6 (6.25%）	3 (3.13%)	3 (3.13%)
~0.80	108 (75.00%)	21 (14.58%）	12 (8.33%)	3 (2.08 %)
~1.00	75 (65.79%)	18 (15.79%）	15 (13.16%)	6 (5.26%)
~1.20	12 (12.50%)	15 (15.63%)	21 (21.87%)	48 (50.00%)

[a] Patients were categorized in quartiles based on the cystatin C (mg/L). [b] Including severe NPDR and PDR. NDR, no diabetic retinopathy; Mild NPDR, mild non-proliferative diabetic retinopathy; Moderate NPDR, moderate non-proliferative diabetic retinopathy; Severe NPDR, severe non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Table 4. Comparison of AUC between different predictive markers.

Predictive markers	*Z value*	*P value (two-sided)*	*95%CI of AUC difference*	
			Lower	*Upper*
Cystatin C and duration of diabetes	-0.5188	0.6039	-0.1176	0.0684
HbA_{1c} and cystatin C	-0.6496	0.5160	-0.1594	0.0800
HbA_{1c} and duration of diabetes	-1.1213	0.2622	-0.1768	0.0481

AUC, area under the curve; HbA_{1c}, glycosylated hemoglobin.

Figure legends:

Fig 1. Cystatin C in patients with NDR, mild NPDR, moderate NPDR, and severe DR. [a] Compared with moderate NPDR (P=0.012), mild NPDR (P=0.001), or NDR (P<0.001), there were significant differences; [b] Compared with NDR (P=0.017), there was a significant difference. NDR, no diabetic retinopathy; Mild NPDR, mild non-proliferative diabetic retinopathy; Moderate NPDR, moderate non-proliferative diabetic retinopathy; Severe NPDR, severe non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Fig. 2. ROC curve of different markers in predicting DR. DR, diabetic retinopathy; HbA1c, and glycosylated hemoglobin.

Fig. 3. ROC curve of cystatin C in predicting severe DR (severe NPDR or PDR). Severe NPDR, severe non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.